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Pathophysiology and management of hemostatic alterations in cirrhosis and liver transplantation

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CHAPTER 1

General introduction and outline of
this thesis



The hemostatic system in cirrhosis

In chronic liver disease such as cirrhosis, the synthetic capacity of the liver is compromised which results in a deficiency of both pro- and antihemostatic proteins. As a result, the hemostatic system in cirrhotic patients is disturbed, yet in a rebalanced state (1). Due to decreased hemostatic proteins on both axis of the hemostatic balance, the rebalanced hemostasis is more vulnerable for decompensation by certain factors such as infection, surgery, and blood loss resulting in either hypo-, or hypercoagulability (Figure 1; Chapter 5). As a result, patients with cirrhosis are not only prone to bleeding, but also prone to develop thromboembolic complications such as deep vein thrombosis, pulmonary embolism, and portal vein thrombosis (2-6).

In patients with cirrhosis, conventional coagulation tests, including the prothrombin time (PT) or international normalized ratio (INR), and the activated partial thromboplastin time (APTT) are often prolonged. These prolonged tests, amongst other factors, have led to the assumption that patients with cirrhosis are hypocoagulable. It has become evident however, that these tests do not adequately represent the hemostatic capacity in these patients, since they only account for the deficiency in procoagulant proteins without taking the deficiency of anticoagulant proteins into account (7). In the clinical setting, these tests fail to predict blood loss and transfusion requirements in patients undergoing orthotopic liver transplantation (OLT) (8), and patients with prolonged PT/APTT are still prone for thrombotic complications. During OLT, patients with prolonged PT/APTT may suffer from hardly any blood loss while patients with relatively normal PT/APTT may experience severe blood loss (9).

Pro- and anticoagulant therapy in patients with cirrhosis

Since conventional coagulation tests do not adequately assess the hemostatic capacity and currently no other reliable laboratory tests are available for daily clinical practice, it remains difficult to assess the true hemostatic state of the cirrhotic patient and to decide for either anti- or pro coagulant therapy. The bleeding- as well as the thrombotic complications occurring in cirrhotic patients indicate a necessity for prophylactic treatment. For instance, prothrombin complex concentrates (PCC) and 1-deamino-8-D-arginine vasopressin (DDAVP) may be effective in the prevention of blood loss during invasive procedures. Anticoagulant therapy such as low molecular weight heparin or direct factor Xa or IIa inhibitors may be helpful in the prevention of portal vein thrombosis (PVT) in cirrhotic patients or hepatic artery thrombosis after OLT. Research on the effect of pro- and anticoagulant drugs on the hemostatic system of cirrhotic patients is essential and can also aid in determining the best dosages for different categories of patients.

The role of portal hypertension in cirrhosis

Besides the altered hemostatic system in cirrhosis, portal hypertension may play a significant role in the development of bleeding during invasive procedures, such as OLT. Portal hypertension causes formation of varices in collateral portal and splanchnic circulation. Around the liver, the increased pressure in local collateral circulation can cause increased blood loss during surgery. It has been demonstrated that a restrictive transfusion policy and maintaining a low central venous pressure (CVP) reduces blood loss and transfusion during OLT (10, 11). While this provides indirect clinical evidence for the contribution of portal hypertension in the bleeding diathesis during OLT, direct evidence is still missing. As currently many centers are maintaining a low central venous pressure (CVP) during OLT and are not routinely correcting pre-operatively prolonged INR by transfusion of fresh frozen plasma (FFP) to avoid aggravation of portal hypertension, research on the efficacy of low-volume hemostatic agents such as PCC is an important next step for the hemostatic management of cirrhotic patients undergoing OLT.

The hemostatic system after OLT

Patients recovering from OLT often display normalization of the PT and APTT as their liver function restores back to normal. However, the relatively high incidence of the early and late postoperative vascular complications and death due to vascular disease suggest a hypercoagulable state (12, 13), likely related to the use of immunosuppressive medication in these patients. Early post-operative assessment of the hemostatic system in patients after OLT indeed has indicated evidence of hypercoagulability (14,15), mostly related to a severe Von Willebrand factor (VWF)/ADAMTS13 dysbalance, overall surgical stress, and as a result of hypofibrinolysis due to increased levels of plasminogen activator inhibitor type 1 (PAI-1). The long term function of the hemostatic system after OLT has not yet been studied.

Outline of this thesis

The scope of this thesis is to further investigate and explore the hemostatic system in the three main clinical stages: the pre-transplant cirrhotic stage, the actual transplant stage, and the long term post-transplant stage. This thesis is therefore divided into three parts, focusing on:

- A)** Hemostatic drugs in patients with cirrhosis
- B)** Blood loss and the prevention of blood loss and transfusion during OLT
- C)** The hemostatic status of the liver transplant recipient

PART A. Hemostatic drugs in patients with cirrhosis

The aim of this section is to gain better understanding of the efficacy and working mechanism of various hemostatic drugs in patients with cirrhosis. DDAVP is a prohemo-

static drug frequently used in patients with hemophilia A and Von Willebrand disease to reduce bleeding during dental or surgical procedures. The working mechanism of DDAVP has been ascribed to the elevation of plasma levels of VWF and Factor VIII (FVIII) (16). It has also been used in patients with cirrhosis, although the efficacy in this patient population is debated. In **Chapter 2** we describe a prospective interventional study in which we investigated the effect of DDAVP on indices of hemostasis after intravenous administration in patients with cirrhosis.

With the increasing recognition of various thrombotic complications in cirrhotic patients, anticoagulant therapy in patients with cirrhosis may be expected. Due to the limited clinical experience in this patient group, the efficacy of various anticoagulant drugs is still unknown. *In vitro* studies have demonstrated that low molecular weight heparin (LMWH) has a more profound anticoagulant effect in plasma from patients with cirrhosis as compared to plasma from healthy controls (17). The possibility of increased response to anticoagulant drugs may have important consequences for the correct dosing in patients with cirrhosis. In **Chapter 3** we describe an *in vitro* study in which we investigated the anticoagulant potencies of unfractionated heparin, LMWH, fondaparinux, dabigatran and rivaroxaban in plasma from patients with cirrhosis.

Adequate monitoring of anticoagulant therapy is essential in patients with cirrhosis considering the fragile hemostatic balance in these patients and the possibility of increased responsiveness to anticoagulant drug. In **Chapter 4** we describe an *in vitro* study that assesses the accuracy of routine monitoring assays on various anticoagulant drugs in plasma from patients with cirrhosis.

PART B. Prevention of blood loss and transfusion during OLT

The aim of this section is to provide more insight in various factors contributing to blood loss during OLT. Due to various developments, blood loss and red blood cell (RBC) transfusion requirements during OLT have significantly decreased in the past decades. However, a relatively low amount of RBC transfusion can still cause an increase in postoperative morbidity and mortality (18). In **Chapter 5** we discuss causes of bleeding during OLT, strategies to prevent blood loss, and treatment possibilities in case severe bleeding does occur.

Hyperfibrinolysis during the anhepatic and the post-reperfusion phase of OLT plays an important role in blood loss. Aprotinin is an antifibrinolytic drug that was frequently used prior to 2007 to reduce blood loss in patients undergoing OLT. The use of aprotinin was discontinued in 2007 after the publication of a study in patients undergoing cardiac surgery, which revealed increased thromboembolic events, mortality, and renal dysfunction associated with the use of aprotinin. In **Chapter 6** we describe a retrospective study that investigated the impact of the discontinuation of aprotinin on blood loss and RBC transfusion requirements during OLT.

Besides the hemostatic alterations, there is emerging evidence that portal hypertension plays a major role in the increased blood loss during OLT. PCC is a low volume hemostatic product containing both pro- and anticoagulant factors, which in theory should strengthen the hemostatic balance without aggravating portal hypertension in patients with cirrhosis. In **Chapter 7** we describe the protocol for a multicenter randomized controlled trial that was designed to investigate the efficacy and safety of PCC in reducing blood loss and RBC transfusion requirements during OLT in patients with cirrhosis. This trial is still ongoing.

In **Chapter 8** we describe a retrospective cohort study in which we aimed to further establish the role of portal hypertension as a contributor to blood loss and RBC transfusion requirements during OLT. For this study we assessed the predictive value of pre-transplant serum markers of portal hypertension regarding intraoperative blood loss and transfusion requirements in patients undergoing OLT.

PART C. The hemostatic status of the liver transplant recipient

The aim of this section is to describe the long term changes in the hemostatic state of liver transplant recipients. While previously it has been demonstrated that patients with end stage liver disease can depict signs of hypocoagulability as well as hypercoagulability before, during, and directly after OLT, literature on the long term effects after liver transplantation is lacking. Adequate assessment of the hemostatic state of liver transplant recipient in the long term is critical for adequate treatment and prevention of vascular disease.

In **Chapter 9** we review and summarize evidence for a hypercoagulable hemostasis as a contributor to thrombotic complications in the liver transplant recipient.

In **Chapter 10** we describe a cross-sectional study in which the hemostatic status of the liver transplant recipient one year after OLT was assessed by measuring indices of hemostasis in plasma from these patients.

In **Chapter 11** the results as described in this thesis are summarized. In **Chapter 12** future perspectives in the field of hemostasis in liver disease and OLT are discussed. **Chapter 13** provides a Dutch summary of this thesis.

In summary, the aims of this thesis were:

- 1) To investigate the efficacy of various anticoagulant drugs, and the reliability of current monitoring assays for these anticoagulant drugs in plasma from patients with cirrhosis.
- 2) To investigate the hemostatic efficacy of DDAVP in patients with cirrhosis.
- 3) To summarize current insights in physiology, prevention and treatment of blood loss during OLT.

- 4) To investigate the contribution of portal hypertension in blood loss during OLT.
- 5) To discuss and investigate the efficacy and safety of PCC and antifibrinolytic therapy in reducing blood loss during OLT.
- 6) To review and summarize evidence for a hypercoagulable hemostatic system in liver transplant recipients.
- 7) To investigate the long-term hemostatic status in liver transplant recipients.

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Part A.
Hemostatic drugs
in patients with
cirrhosis



